

令和2年度
広島大学第一内科
同門会専修医奨励賞

JA尾道総合病院 消化器内科

栗原 啓介

略歴



平成14年	4月	広島大学医学部入学
平成20年	3月	広島大学医学部卒業
平成20年	4月	広島市立広島市民病院 初期研修
平成22年	4月	広島市立広島市民病院 消化器内科
平成25年	4月	広島大学病院 消化器・代謝内科
令和1年	4月	尾道総合病院 消化器内科
令和3年	1月	同上

JA尾道総合病院



当院は尾道市に位置し393床を有し、広島県尾三医療圏の基幹病院として20～30km圏の広域に高度医療を提供。尾道市、三原市を中心に北は世羅町、南はしまなみの島々まで対応しています。

現在は新型コロナウイルス感染患者の入院受け入れも行いながら救急ならびに日常診療に従事しています。



田妻 進 院長



病院紹介①

尾道総合病院 消化器内科

2020年内視鏡検査実績

(2020/1/1～2020/12/31)

検査種別	検査数
上部内視鏡（観察）	6577
上部EMR・ESD	123
下部内視鏡（観察）	1778
下部EMR	457
下部ESD	45
カプセル内視鏡	28
小腸内視鏡（観察）	9
EVL	36
ERCP	782
EUS	909
EUS-FNA	85

尾道総合病院消化器内科の
2020年内視鏡実績です。

2020年は新型コロナ感染症
の影響もあり5～6月にか
けて検査数を抑えていま
したが、それでも1年間
を通じて多くの検査・処
置を行っています。

病院紹介② 早期膵癌診断プロジェクト

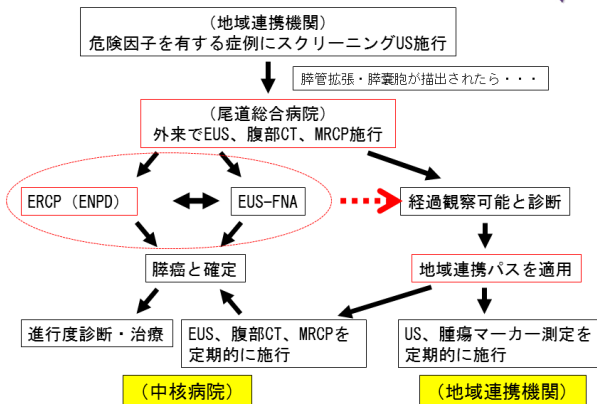
2020年に当院で膵癌と診断された患者数合計 63例

Stage 0	1例	手術	13例
Stage IA	2例	化学療法	33例
Stage IB	2例	BSC	17例
Stage IIA	12例		
Stage IIB	11例		
Stage III	7例		
Stage IV	28例		

当院では膵癌診断プロジェクトを通じて膵癌診断・治療に力を入れており2020年は合計63例の膵癌患者を新規に診断しています。多くは化学療法の適応となる進行膵癌ですがStage 0の早期膵癌も認めています。

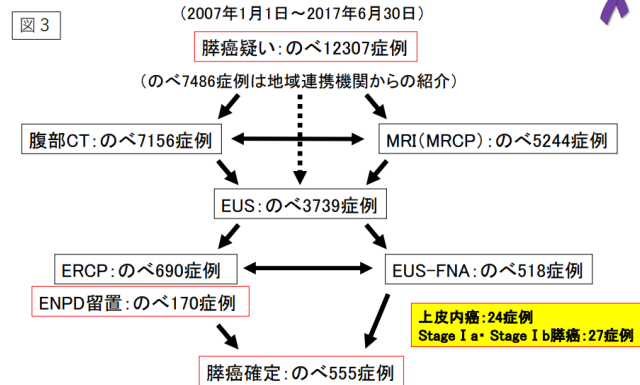
出典：尾道総合病院ホームページ 膵癌プロジェクト
http://onomichi-gh.jp/cancer_med/pancreatic_cancer/index.php

尾道市医師会膵癌早期診断プロジェクト



Onomichi Medical Association

プロジェクトの成績



(花田敬士ほか 日消誌 2018)
 Onomichi General Hospital

病診連携を基軸とした『膵癌の早期診断の体制作り』として2007年より開始。中核病院から地域連携施設に、“膵癌診療ガイドライン”に記載される危険因子を啓発し、超音波内視鏡（EUS）、磁気共鳴胆管膵管造影（MRCP）の有用性、腹部超音波（US）での軽微な膵管拡張の重要性を啓発。連携施設では、危険因子を有する症例等を中心にUSを施行し、異常所見を認めた場合には中核病院に積極的に紹介し精査を行う流れを確立。

発表・論文実績

～発表歴～

(2019/11～2020/10)

- American Pancreatic Association, Maui, Poster

K Kurihara, K Hanada, A Shimizu.

「The values of Serial Pancreatic Juice Aspiration Cytologic Examination (SPACE) in the Early Detection of Pancreatic Cancer」

- 第99回 日本内視鏡学会総会, International Symposium

K Kurihara, K Hanada, A Shimizu.

「The role of endoscopy for the management of pancreatic cystic lesions」

- 第56回 日本胆道学会学術集会, International Symposium

K Kurihara, K Hanada, S Tazuma.

「The values of ENGBD and EUS-FNA in the preoperative diagnosis of gallbladder lesions」

- 第55回 日本胆道学会学術集会, パネルディスカッション

栗原啓介、花田敬士、田妻進.

「胆嚢病変の術前良悪性診断のためのENGBDとEUS-FNA」

- DDW 2020, Chicago, Oral presentation

K Hanada, M Yokode, **K Kurihara**, A Shimizu, M Ikeda, T Abe, S Yonehara.

「Clinicopathological features of flat type and low papillary type in Stage 0/IA pancreatic ductal adenocarcinoma」

～論文～

(2019/11～2020/12)

K Kurihara, K Hanada, et al. Investigation of Fluorodeoxyglucose Positron Emission Tomography for the Diagnosis of Solid Pseudopapillary Neoplasm of the Pancreas: A Study Associated With a National Survey of Solid Pseudopapillary Neoplasms. *Pancreas*. 2019; 48: 1312-1320.

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K Kurihara, K Hanada, et al. Investigation of Fluorodeoxyglucose Positron Emission Tomography for the Diagnosis of Solid Pseudopapillary Neoplasm of the Pancreas: A Study Associated With a National Survey of Solid Pseudopapillary Neoplasms. *Pancreas*. 2019; 48: 1312-1320.

Abstract

Objectives: To investigate the utility of Fluorodeoxyglucose positron emission tomography (FDG-PET) for Solid-pseudopapillary neoplasm (SPN) diagnosis.

Methods: The subjects included 53 cases of SPN. We compared the maximum standardized uptake volume (SUVmax) to those of 25 cases of pancreatic duct cancer (PDC) and 18 cases of pancreatic neuroendocrine neoplasm (PNEN). In addition, immunopathological testing for SPN were undertaken with regard to FDG uptake.

Results: An increase in SUVmax was observed in all tumors with increased tumor diameter. Among tumors of 20 mm or smaller, the SUVmax of SPN was significantly higher than those of PDC and PNEN. The results of a pathological study of FDG uptake in SPN revealed increased glucose transporter protein type 1 (GLUT1) expression with tumor enlargement. Furthermore, widespread necrosis along with tumor enlargement and increased hypoxia-inducible factor (HIF)-1 and vascular endothelial growth factor (VEGF) expression under hypoxic conditions were observed in the areas of necrosis.

Conclusions: In cases in which high FDG uptake is observed in small pancreatic tumors, FDG-PET is potentially useful for SPN differentiation. The factors involved in FDG uptake in SPN include cell density and GLUT1 expression, as well as HIF-1 and VEGF expression in the hypoxic environment of necrotic areas.

ORIGINAL ARTICLE

OPEN

Investigation of Fluorodeoxyglucose Positron Emission Tomography for the Diagnosis of Solid Pseudopapillary Neoplasm of the Pancreas *A Study Associated With a National Survey of Solid Pseudopapillary Neoplasms*

Keisuke Kurihara, MD,* Keiji Hanada, MD, PhD,† Masahiro Serikawa, MD, PhD,* Yasutaka Ishii, MD, PhD,* Tomofumi Tsuboi, MD, PhD,* Ryota Kawamura, MD,* Tsuyoshi Sekitou, MD,* Shinya Nakamura, MD,* Takeshi Mori, MD,* Tetsuro Hirano, MD,* Juri Ikemoto, MD,* and Kazuaki Chayama, MD, PhD*

Objectives: This study aimed to investigate the utility of fluorodeoxyglucose (FDG) positron emission tomography for solid pseudopapillary neoplasm (SPN) diagnosis.

Methods: The subjects included 53 cases of SPN. We compared the maximal standardized uptake volume (SUVmax) with those of 25 cases of pancreatic duct cancer and 18 cases of pancreatic neuroendocrine neoplasm. In addition, immunopathological testing for SPN with regard to FDG uptake was undertaken.

Results: An increase in SUVmax was observed in all tumors with increased tumor diameter. Among tumors of 20 mm or smaller, the SUVmax of SPN was significantly higher than those of pancreatic duct cancer and pancreatic neuroendocrine neoplasm. The results of a pathological study of FDG uptake in SPN revealed increased glucose transporter protein type 1 expression with tumor enlargement. Furthermore, increased hypoxia-inducible factor-1 and vascular endothelial growth factor expression under hypoxic conditions were observed in the areas of necrosis.

Conclusions: In cases in which high FDG uptake is observed in small pancreatic tumors, FDG positron emission tomography is potentially useful for SPN differentiation. The factors involved in FDG uptake in SPN include cell density and glucose transporter protein expression, as well as hypoxia-inducible factor and vascular endothelial growth factor expression in the hypoxic environment of necrotic areas.

Key Words: solid pseudopapillary neoplasm, FDG-PET, pancreas, pancreatic duct cancer, pancreatic neuroendocrine neoplasm, tumor

Abbreviations: FDG-PET - fluorodeoxyglucose positron emission tomography, SPN - solid pseudopapillary neoplasm, SUVmax - maximal standardized uptake volume

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PDC - pancreatic duct cancer, PNEN - pancreatic neuroendocrine neoplasm, GLUT1 - glucose transporter protein type 1, HIF - hypoxia-inducible factor, VEGF - vascular endothelial growth factor, JPS - Japan Pancreas Society, CT - contrast computed tomography (*Pancreas* 2019;48: 1312-1320)

Solid pseudopapillary neoplasm (SPN) in the pancreas is a relatively rare pancreatic epithelial tumor that often occurs in young women and is reported to occur in 0.17% to 2.7% of all pancreatic tumors.¹ With advances in imaging examinations, reports of SPN have increased in recent years.²⁻⁵ We conducted our own investigation using data from the Japan Pancreas Society (JPS) SPN National Survey to study the clinical pathology of this disease. The results of the National Survey revealed that the typical macroscopic findings of SPN included a mixture of cysts and solid components, calcification, and bleeding. Contrast computed tomography (CT) examinations revealed prolonged, uneven staining, with tumors depicted with cysts and calcification. However, in small SPNs, the tumors may not have cysts, calcification, or bleeding. Therefore, it is often difficult to differentiate SPN from pancreatic duct cancer (PDC).²

Fluorodeoxyglucose positron emission tomography (FDG-PET) is useful for the differential diagnosis of malignancies or otherwise of tumorous lesions in various organs. In pancreatic tumors, high FDG uptake is observed in PDC; thus, it has been reported as a marker of malignancy.⁶ Furthermore, although World Health Organization classifications consider SPN to have low malignant potential, there are many reports of high FDG uptake.⁷⁻¹³

The degree of FDG uptake by tumors generally depends on the tumor size, histologic type, and microvessel density at the molecular level,⁶ and associations have been reported with glucose transporter-1 (GLUT-1) related to glucose metabolism,¹³⁻¹⁵ hypoxia-inducible factor-1 (HIF-1) related to hypoxic environments, and vascular endothelial growth factor (VEGF) related to neovascularization.¹⁶⁻²⁰

A National Survey of SPN of the pancreas was conducted by the JPS; we additionally conducted a study to clarify the utility of FDG-PET for the diagnosis of SPN, as well as an investigation of the molecular mechanisms related to FDG uptake.

Committee

The JPS established a committee (Drs Keiji Hanada, Keisuke Kurihara, Takao Itoi, Akio Katanuma, Tamio Sasaki, and Kazuo Hara as endoscopists; Drs Masafumi Nakamura, Wataru Kimura

【はじめに】 膵Solid-pseudopapillary neoplasm(SPN)は若年女性に好発する比較的稀な膵上皮性腫瘍で膵腫瘍全体の0.17-2.7%を占める。画像検査の進歩により近年SPNの報告は増え、著者も日本膵臓学会によるSPN全国調査に参加し臨床病理学的特徴の検討を行った。SPNはWHO分類で低悪性度と位置付けられているにもかかわらずFluorodeoxyglucose positron emission tomography(FDG-PET)においてFDGの高集積が認められるとの報告が多く、SPN全国調査でも同様の結果であった。本論文ではSPN診断におけるFDG-PETの有用性を明らかにするとともに、FDG集積に関与する分子機構の検討を行った。

【方法】 全国調査におけるSPN 288例のうち、FDG-PETが撮影された53例を対象とし、当院で手術された膵管癌25例、Pancreatic neuroendocrine neoplasm(PNEN)18例とmaximum standardized uptake volume(SUV max)の比較を行った(Table. 2)。また当院で手術されたSPN 6例についてFDG集積に関してGLUT-1, VEGF, HIF-1, CD31の免疫染色を行い病理学的な検討を行った。

全国調査でFDG-PETが撮影されたSPN患者は53例であった。男女比は22:31、平均年齢は 37.5 ± 12.4 歳(11-68歳)、局在は膵頭部15例、膵体部25例、膵尾部13例であった。平均腫瘍径は 38.4 ± 28.2 mm(10-130mm)であった。CTでは35例(66%)で遷延性濃染を認め、石灰化は32例(60%)、嚢胞は22例(42%)に認めた。腫瘍径が20mm以下の症例は15例あり、そのうち9例は嚢胞と石灰化のいずれも認めず、画像上は膵管癌やPNENとの鑑別が困難であった。

【結果】 SPNのSUVmaxの中央値は4.4(1.8-9.8), 平均値は 4.9 ± 2.6 であった. SUVmaxの一般的なカットオフ値である3を基準に陽性率を判断するとFDG-PET陽性例は41例(77%)であった. また20mm以下のSPNでも15例中9例(60%)がFDG-PET陽性であった. SPNの腫瘍径とSUVmaxの関係について統計学的に検討すると正の相関が認められた.

SPNと膵管癌, PNENのSUVmaxを比較すると膵管癌のSUVmaxがSPNより有意に高く, PNENはSPNと有意差は認めなかった. 一方, 20mm以下の腫瘍ではSPNのSUVmaxは膵管癌, PNENと比較して有意に高く, 小型の膵腫瘍ではFDG-PETがSPNの鑑別に有用な可能性がある. またSPNのFDG集積に関する病理学的検討ではSPNでは細胞密度が高いことが関係していると考えられた. 免疫染色では腫瘍の増大とともにGLUT1の発現の上昇を認めたが, 腫瘍の増大とともに壊死が広範囲に出現し, 壊死部では低酸素下におけるHIF-1やVEGFの発現の上昇を認めたが, その一方で広範囲に及んだ壊死部では細胞密度が低下しFDGの集積も低下しSUVmaxの上昇が抑えられると考えられた.

【結論】 結論として小さな膵腫瘍でFDGの高集積が認められる場合はSPNの鑑別に有用な可能性がある. SPNのFDG集積にはその高い細胞密度とGLUT1の発現が関係していると考えられ, 壊死部では低酸素環境下におけるHIF-1, VEGFの発現が増強しているが広範囲に及ぶ壊死がSUVmaxの上昇を抑えると考えられる.

TABLE 2. Comparison of SUVmax Between SPN, PDC, and PNEN

	SPN	PDC	P	PNEN	P
No. patients, n	53	20		18	
SUVmax, mean	4.9	6.0	0.04	4.4	0.43
SUVmax for each tumor diameter, mm					
≤20	3.9	2.4	0.02	2.6	0.02
21–30	4.6	6.5		4.2	
≥40	5.6	8.7		9.4	

表2. 患者背景

対象となるSPN, 膵癌(PDC), 膵内分泌腫瘍(PNEN)の腫瘍径とFDG-PETにおけるSUVmax値の比較

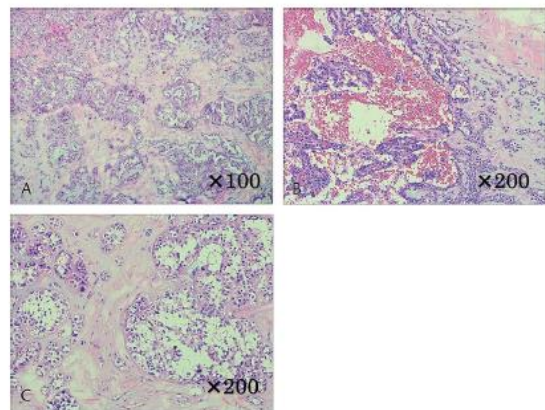


FIGURE 3. Histological findings of case 6. A and B, Necrotic changes were widespread within the tumor, with widespread findings of bleeding also observed. C, Large-scale follicular degeneration in the intercellular spaces of the area of necrosis, with some cyst formation, and reduced cell density in the areas of necrosis.

図3. 腫瘍径の大きなSPNの病理組織像

大型なSPNは腫瘍中心部にかけて広範囲に囊胞変性、壊死変性を伴っている

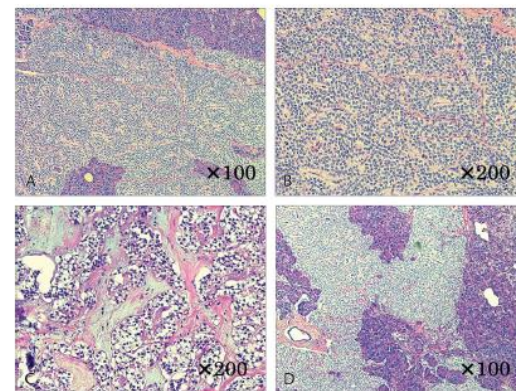


FIGURE 2. Histological findings of case 1. A and B, Monomorphic epithelial cells cohered in high density and forming solid and pseudopapillary structures. C, Small areas of necrosis in the middle of the tumor, which included a number of instances of small-scale follicular degeneration of the tumor cells. D, Involvement of the surrounding pancreatic tissue was observed in areas with no septum.

図2. 腫瘍径の小さなSPNの病理組織像

小型なSPNは細胞密度が高く腫瘍中心部には局限して囊胞変性・壊死変性を伴っている

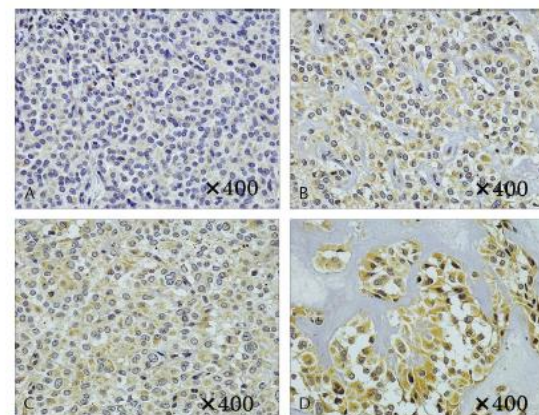


FIGURE 5. Immunostaining of HIF-1. A and B, Case 1. A, No cytoplasmic staining in the solid area. B, Weak cytoplasmic staining in the area of necrosis. C and D, Case 6. C, Weak cytoplasmic staining in the solid area. D, Strong cytoplasmic staining in the area of necrosis.

図5. HIF-1染色

腫瘍の増大とともに壊死が広範囲に出現し、壊死部では低酸素下におけるHIF-1発現の上昇を認めた

K Kurihara, K Hanada, A Shimizu. Endoscopic Ultrasonography Diagnosis of Early Pancreatic Cancer. *Diagnostics*. 2020; 10, 1086.

Abstract

Early diagnosis of pancreatic cancer (PC) can improve patients' prognosis. We aimed to investigate the utility of endoscopic ultrasonography (EUS) for the early diagnosis of PC. This study included 64 patients with PC at an early stage treated at Onomichi General Hospital between January 2007 and January 2020. Diagnostic procedures included contrast computed tomography (CT), magnetic resonance cholangiopancreatography, EUS fine-needle aspiration, and endoscopic retrograde cholangiopancreatography (ERCP) for pancreatic juice cytology. The mean age was 71.3 years. In all, 32 patients were stage 0, and 32 were stage I. As for image findings, the main pancreatic duct (MPD) stenosis was detected in several cases, although CT and MRCP seldom detected tumors. EUS had a high detection rate for stage 0 tumor lesions. The median observation period was 3.9 years. In cases with stage 0, the 1 year and 5 year survival rates were 100% and 78.9%, respectively. In cases with stage I, the 1 year and 5 year survival rates were 96.4% and 66.7%, respectively. EUS has the highest sensitivity among all imaging modalities for detecting small pancreatic tumors. Cases with MPD dilation or stenosis, especially with tumors that cannot be identified on CT and MRI, should have EUS performed. In some cases, EUS was not able to detect any tumor lesions, and ERCP-based pancreatic juice cytology should be useful for pathological diagnosis.



Article

Endoscopic Ultrasonography Diagnosis of Early Pancreatic Cancer [†]

Keisuke Kurihara *, Keiji Hanada and Akinori Shimizu

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[†] This study was approved by the ethics committees of Onomichi General Hospital (OJH-202043).

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Abstract: Early diagnosis of pancreatic cancer (PC) can improve patients' prognosis. We aimed to investigate the utility of endoscopic ultrasonography (EUS) for the early diagnosis of PC. This study included 64 patients with PC at an early stage treated at Onomichi General Hospital between January 2007 and January 2020. Diagnostic procedures included contrast computed tomography (CT), magnetic resonance cholangiopancreatography, EUS fine-needle aspiration, and endoscopic retrograde cholangiopancreatography (ERCP) for pancreatic juice cytology. The mean age was 71.3 years. In all, 32 patients were stage 0, and 32 were stage I. As for image findings, the main pancreatic duct (MPD) stenosis was detected in several cases, although CT and MRCP seldom detected tumors. EUS had a high detection rate for stage 0 tumor lesions. The median observation period was 3.9 years. In cases with stage 0, the 1 year and 5 year survival rates were 100% and 78.9%, respectively. In cases with stage I, the 1 year and 5 year survival rates were 96.4% and 66.7%, respectively. EUS has the highest sensitivity among all imaging modalities for detecting small pancreatic tumors. Cases with MPD dilation or stenosis, especially with tumors that cannot be identified on CT and MRI, should have EUS performed. In some cases, EUS was not able to detect any tumor lesions, and ERCP-based pancreatic juice cytology should be useful for pathological diagnosis.

Keywords: endoscopic ultrasonography; pancreatic cancer; early diagnosis

1. Introduction

According to the Vital Statistics of Japan reported by the Ministry of Health, Labor, and Welfare [1], 40,981 patients were diagnosed with pancreatic cancer (PC) in 2017, and the number is increasing yearly. In 2018, 35,390 patients died of PC, and the mortality rate was 29.7 per 100,000 men and 27.4 per 100,000 women. PC has the fourth highest mortality rate of all cancers in Japan, and the 5 year survival rate is 8.7%. The poor prognosis is attributed to the difficulty in diagnosing PC at an early stage; it is usually diagnosed at an advanced stage [2,3]. However, when PC is diagnosed at an early stage, it has a good prognosis. According to an analysis from the Japan Pancreatic Cancer Registry, the 5 year survival rates of patients with Union for International Cancer Control (UICC) stage IA and stage 0 were 68.4% and 85.8%, respectively [4].

We developed an initiative for the early detection of PC, which involved collaboration between PC specialists from medical centers and general practitioners [5]. The specialists used endoscopic ultrasonography (EUS) in addition to contrast computed tomography (CT) and magnetic resonance imaging (MRI). EUS is an ultrasound technique in which the tip of the endoscope is equipped with a high-frequency transducer. EUS has a high resolution, and there are many reports of its high sensitivity for detecting PC. In this study, we aimed to investigate the clinical features of early-stage PC and the utility of EUS for diagnosing early-stage PC.

【はじめに】 膵癌の予後改善には早期発見が重要である. 今回、自施設で経験したStage 0, Stage I 膵癌の臨床的特徴と膵癌早期発見における超音波内視鏡(EUS)の有用性を検討した.

【方法】 2007年1月から2020年1月に尾道総合病院で手術施行されたStage 0, Stage Iの膵癌患者64例を対象として臨床的特徴と画像検査(CT, MRI, EUS)での病変検出率とEUSの画像的特徴に関して検討を行った.

【結果】 術後病理結果から32例はStage 0, 32例はStage Iの診断であった. 術後平均観察期間は3.9年でStage 0膵癌の1年生存率, 5年生存率はそれぞれ100%, 78.9%と高い値であった. 画像的特徴として膵管狭窄を認め, いずれの画像検査でも検出可能であった. 一方, CTやMRIでは腫瘍の検出率は低くEUSが最も高い検出率であった. Stage 0においても腫瘍を同定する症例を認めたが, Stage 0 膵癌における腫瘍は癌周囲に生じた炎症性変化を見ている可能性が示唆される. EUSで腫瘍同定が困難な症例では膵液細胞診により膵癌の診断に至った症例を認めた.

【結語】 Stage 0膵癌は良好な予後を認め, 膵癌予後改善には早期発見が重要と考える. 画像検査では膵管狭窄を伴う症例が多いがCTやMRIでは腫瘍の検出率は低く, EUSが最も高い検出率であった. 膵癌を疑う膵管狭窄を伴う症例には積極的にEUSを施行することが重要である.

Table 1. Risk factors for pancreatic cancer.

- Family history
- Pancreatic cancer
- Hereditary pancreatic cancer syndrome
- Accompanying diseases
- Diabetes mellitus
- Obesity
- Chronic pancreatitis
- Hereditary pancreatitis
- Intraductal papillary mucinous neoplasm
- Pancreatic cyst
- Habits
- Tobacco use
- Heavy drinking

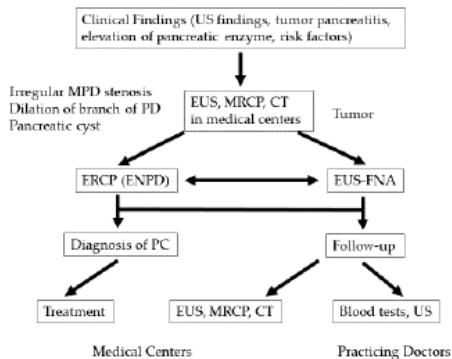


表1. 膵癌リスク因子と膵癌診断におけるストラテジー

Table 2. The clinical characteristics of stage 0 and stage I PC.

	All Cases (n = 64)	Stage 0 (n = 32)	Stage I (n = 32)
Sex (male/female)	33/31	19/13	14/18
Age, mean (range)	71.3 (38–87)	71.3 (52–87)	71.8 (39–84)
Observation period (year), median (range)	3.9 (0.5–12.7)	4.2 (1.7–12.7)	3.4 (0.5–10.7)
Location, head/body/tail, n	25/32/7	11/16/5	14/16/2
1 year survival rate (%)		100	96.4
5 year survival rate (%)		78.9	66.7

表2. 対象患者の患者背景、予後

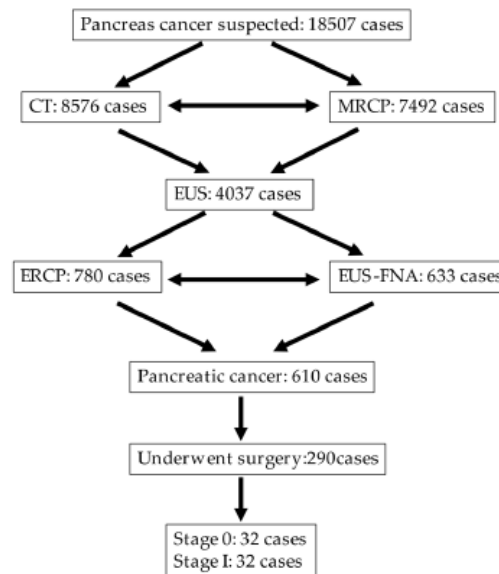


Figure 2. The flow of patient information. ENPD: endoscopic nasopancreatic drainage, ERCP: endoscopic retrograde cholangiopancreatography, EUS: endoscopic ultrasonography, FNA: fine-needle aspiration, MRCP: magnetic resonance cholangiopancreatography.

図2. 当院における膵癌患者診断のフローチャート

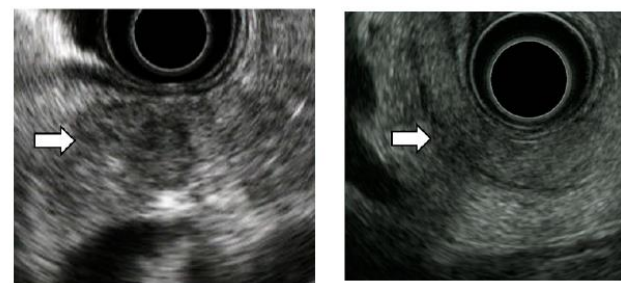


Figure 3. EUS imaging findings of stage 0 PC. Ten cases of stage 0 PC had hypoechoic lesions around MPD stenosis. Six cases showed a well circumscribed hypoechoic lesion (a). The other four cases showed a pale hypoechoic lesion with a relatively circumscribed lesion (b).

図3. Stage 0 膵癌におけるEUS所見

膵管狭窄周囲に腫瘍を認めるが、膵癌周囲の炎症を反映している可能性が示唆される